REMARKS

Claims 1-41 are pending in the present application. Claims 1 and 21 have been amended to recite that certain steps of the method be performed using an automated device; i.e., automated synthesis. This amendment finds support in the specification. (See, for example, Examples 3 - 8). No new matter has been added.

Claims 1-41 stand rejected under 35 U.S.C.§103(a) as allegedly obvious over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar") in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers") and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler") and further in view of Sproat et al. (PTO-892 Ref.W), Conway, et al. (PTO-892 Ref.Y), Atkinson et al. (PTO-892 Ref.Z), and Sproat et al. (PTO-892 Ref. RA). Applicants respectfully request reconsideration and withdrawal of the rejection as the amended claims are directed to automated syntheses, which were heretofore thought to require precise methodology with respect to the solvents employed.

Automated oligonucleotide synthesis regimes are known in the art to require specific conditions of time, temperature, reagent and solvent at each deprotection and coupling step. This is because even a slight departure from the optimal conditions provided in published regimes can introduce reductions in yield that, given the iterative nature of the synthesis, can reduce the overall yield of the synthesis (and, obviously, the purity of the product) to the point where the product is unsuitable for intended uses such as, for example, research or pharmaceutical applications. Thus, practitioners in the art typically exercise great care not to deviate from standard automated synthetic protocols.

The present invention is directed to automated synthetic procedures for phosphorus-linked oligomers wherein protic acids dissolved in aromatic solvents are used to deprotect the 5'-hydroxyl group. The use of these solvents provides excellent safety, environmental, and economic benefits over methods of the prior art. Applicants have

discovered that the deprotection of oligonucleotide synthons can be successfully performed using solvents other than the halogenated alkyl solvents, such as dichloromethane, that are currently used in automated solid phase oligonucleotide synthesis regimes, with yields that are comparable to those of existing solid phase oligonucleotide synthesis protocols.

There is nothing in the art cited by the Office Action that would suggest the desirability of modifying the customary deprotection protocols used in automated oligonucleotide synthesis. In addition, there also is no disclosure or suggestion in the cited art that such modification would result in a synthetic protocol having adequate yield of oligomeric product.

As will be recognized, claims cannot be found obvious in view of prior art unless the references themselves suggest that their respective teachings should be modified in a way that would produce the claimed invention. *Berghauser v. Dann*, 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make any necessary modifications. *In re Stencel*, 4 U.S.P.Q.2d 1071, 1073 (Fed. Cir. 1987), *accord*, *Ex parte Marinaccio*, 10 U.S.P.Q.2d 1719 (Pat. Off. Bd. App. 1989). In this respect, the following statement by the Patent Office Board of Appeals is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." .....Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would ***impel*** one skilled in the art to do what the patent applicant has done.

Ex parte Levengood, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) (citations omitted; emphasis added).

Significantly, the Office Action identifies no "motivating force" that would have "impelled" persons of ordinary skill to modify the teachings of the cited art to arrive at Applicants' claimed invention.

As discussed above, it is well known in the art of automated oligonucleotide synthesis that the efficiencies of the individual nucleotide couplings must be extremely high to provide a useful product. As disclosed in the Gait reference, Table 2 on page 17 provides theoretical overall yields as a function of the number of nucleotide couplings for oligonucleotides. It can be seen, for example, that for a 20-mer, where the yield of each individual coupling step is 99%, the overall yield of 20-mer oligonucleotide is 81.8%. However, the table shows that even a small decrease in yield of the individual couplings to 95% results in a drastic reduction in the overall yield to 35.8%. A further decrease in yield of the individual couplings to 90% results in an overall yield of only 12.2%, and a further decrease in yield of the individual couplings to 80% results in an overall yield of only 1.2% Such low overall yields would not be practical for commercial synthesis of oligonucleotides. Oligonucleotide Synthesis, a Practical Approach, Gait, M.J., Ed. IRL Press, 1996 (a copy of this reference was provided in Applicants' response filed July 6, 1999.)

It is therefore apparent that maintenance of very high efficiency (*i.e.*, yield) is critical to successful oligonucleotide syntheses. *See, e.g.*, Sinha, *Large Scale Oligonucleotide Synthesis Using the Solid-Phase Approach,* **1993**, Protocols for Oligonucleotide and Analogs, Agrawal, Ed. Ch. 18, p. 439 ("the aim of a good synthetic strategy is to obtain almost quantitative reactions at each step.") Paul *et al.* teach that "high product yields from oligonucleotide synthesis require quantitative removal of the dimethoxytrityl (DMT) group during the deblocking step." *Nucleic Acids Research*, **1996**, Vol. 24, 15, p. 3048. Paul *et al.* also teaches that most common solvents, such as acetonitrile,

when used in combination with protic acids for the deprotection step **interfere** with the deprotection step, which causes a decrease in yield. Paul *et al.* suggests that this interference "may explain why methylene chloride has remained the preferred solvent for deblocking oligonucleotides." *Id.* at 3051.

In addition, the Gait reference further demonstrates the criticality of even small details in established oligonucleotide synthetic protocols, providing that

> [it] should be recognized that [in] a chemical synthesis method . . . a very slight change to a material or method can often make the difference between barely obtaining a usable product and ensuring routinely reliable synthesis.

Oligonucleotide Synthesis, A Practical Approach, ed. Gait.

The Gait reference further states at pages 18-19 that solvent variations can severely impact product yield. Given the Gait reference's disclosure of the sensitivity of oligomer yield to solvent composition, one skilled in the art of oligonucleotide synthesis would not be motivated to change the solvents customarily used in established protocols for automated solid phase oligonucleotide synthesis. None of the cited prior art suggests that employing the solvents of the present invention in the deprotection step would not significantly effect the yield. Indeed, the Paul reference cited above teaches that many common solvents would significantly effect the yield. Therefore, without the benefit of Applicants' disclosure, the art skilled would not have been motivated to modify the cited references as suggested by the Office Action.

Significantly, none of the cited prior art references suggests the desirability of the use of the solvents of the present invention for use in the deprotection step in an automatic oligonucleotide synthetic regime as is presently claimed, despite their superior environmental, economic, and safety benefits over the solvents used in the prior art (*e.g.*, methylene chloride). Although the Office Action states that the cited prior art suggests a "whatever works best" approach

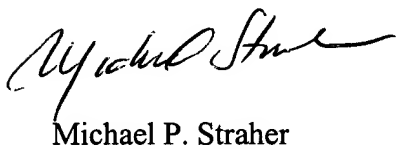
and that this "suggestion" would motivate the art skilled to employ solvents such as those claimed in the present invention for the deprotection step, none of these statements in the cited art are in the context of **automated oligonucleotide synthesis**. Moreover, the standard apparently applied by the Office Action is *not* the appropriate standard for an obviousness determination. It is settled law that the "mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art *suggested the desirability of the modification.*" *See, In re Laskowski*, 10 USPQ 2d 1397, 1399 (Fed. Cir. 1989)(emphasis added.) At most, the cited references disclose that the art skilled might have found it *obvious to try* various solvents (and Applicants do not even concede this, especially in light of the teachings of the Paul reference). However, "whether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *See, In re Fine*, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988)(citations omitted.) As stated above, a reasonable likelihood of success must exist that can be gleaned from the prior art, and not from the hindsight provided by Applicants' invention. *See, Northern Telcom, Inc. v. Datapoint Corp.,* 15 USPQ 1321, 1323, (Fed. Cir. 1990).

As the cited art does not teach or suggest Applicants' claimed invention, and does not provide motivation to use the same with a reasonable expectation of success of achieving the high yields encountered by customary oligonucleotide synthesis protocols, Applicants' claimed invention is not obvious in view of this art. Accordingly, Applicants respectfully request withdrawal of this rejection.

Applicants believe that the claims are in condition for allowance. An early Office

Action to that effect is, therefore, earnestly solicited.

Respectfully Submitted,



Date: December 22, 2000

Michael P. Straher
Registration No: 38,325

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Tel: (215) 568-3100
Fax: (215) 568-3439